

# **Impact of Twin-to-Twin Transfusion Syndrome, Preterm Birth, and Vision Loss on Development**

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**Abstract:** This study compared the developmental outcomes of twin boys (one who is blind and one who is sighted) who were born prematurely and diagnosed with twin-to-twin transfusion syndrome (TTTS) at age 24 months. The results indicate a disparity in the developmental outcomes of the twins. Although the medical risk factors that are associated with TTTS and preterm births, as well as vision loss, appear to have a negative impact on developmental outcomes, it is impossible to determine the degree to which any factor is responsible for this result.

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Twin-to-twin transfusion syndrome (TTTS) is a rare condition with no identified cause. It occurs in identical twin pregnancies as a result of a disproportionate blood flow between the infants through the connecting blood vessels in their shared placenta (Allen, Garabelis, Bornick, & Quintero, 2000; Elliott, 1990; Hecher, Plath, Bregenzer, Hansmann, & Hackeloer, 1999; Shah & Chaffin, 1989). The disproportionate flow of blood commonly causes a disparity in growth between the two infants that can be as great as 25% or more. The infant who receives too much blood is typically the larger of the two and is referred to as the "recipient" twin, and the infant who receives too little blood is the smaller and is referred to as the "donor" twin (Allen et al., 2000; Elliott, 1990; Farley, Cox, & Long, 2000; Mari, Detti, Oz, & Abuhamad, 2000; Mari et al., 2001; Ville, Hyett, Hecher, &

Nicolaides, 1995). Intra-uterine growth restriction (IUGR), a birth weight at or below the 10th percentile for gestational age and sex, imparts a significantly increased risk of adverse neurodevelopmental outcomes. It is the second leading cause of perinatal morbidity and mortality, preceded only by prematurity (Bernstein, & Gabbe, 1996; Demasio & Bahado-Singh, 2002; Gray, O'Callaghan, Harvey, Burke, & Payton, 1999; Peleg, Kennedy, & Hunter, 1998; Resnik, 2002). Among the many risks associated with TTTS are preterm birth and retinopathy of prematurity.

This article reviews the literature on the effects of TTTS, preterm birth, and visual impairment on developmental outcomes and reports on a study of the developmental outcomes of twin boys, who were born at 26 weeks gestational age and were diagnosed with TTTS at age 24 months. One twin was subject to the most severe medical risk factors that are associated with TTTS and preterm birth, including total blindness that was due to retinopathy of prematurity (ROP), while the medical risk factors experienced by the other twin did not appear to have lasting developmental effects.

## **Review of the literature**

### **TTTS and IUGR**

The incidence of TTTS appears to be uniform worldwide, striking about 10% of all identical twin pregnancies with a mortality rate of 60%–100% (approximately 4,000 infants per year). There is a higher survival rate for the recipient twin than for the donor twin (Allen et al., 2000; Bajoria, Wigglesworth, & Fisk, 1995; Denbow et al., 1998; Farley et al., 2000; Mari et al., 2001; Ville et al., 1995; Zach & Ford, 2002).

The increased risk of infant mortality that is due to perinatal

complications and IUGR underscores the importance of early diagnosis and treatment (Demasio & Bahado-Singh, 2002). TTTS is usually diagnosed by ultrasound in the second trimester, at which time the configuration of the amniotic sacs, volume of amniotic fluid, and placental vascularization can be distinguished, and the recipient and donor twins can be identified. Ultrasound is used not only to diagnose TTTS, but to monitor and plan intervention (Allen et al., 2000; Farley et al., 2000; Mari et al., 2001; Peleg et al., 1998; Resnik, 2002; Shah & Chaffin, 1989; Zach & Ford, 2002). The selection of treatments and the timing of their delivery are determined on the basis of the severity of TTTS, the viability of the infants, the risk to the mother, potential fetal damage leading to long-term disabilities, and the availability of treatment methods (Farley et al., 2000).

In viable pregnancies, preterm delivery is a consideration, the risks of which must be weighed against the effects of the infants' extended exposure to the TTTS intrauterine environment (Peleg et al., 1998; Resnik, 2002). Several treatment options are available. Fetoscopic placental laser therapy is conducted in an effort to sever the vascular connections between the twins' bloodstreams. The treatment requires identification of the shared blood vessels on the placental surface through fetoscopy and then the "disconnection" of the twins' vascular connections through laser surgery. This method offers the only "cure" for TTTS. If successful, it is needed only once. The risk of long-term neurological damage is lower with this treatment than with others. In 90% of the cases, at least one twin survives, and in 68% of the cases, both twins do (Allen et al., 2000; Farley et al., 2000; Slaman-Forsythe, 2000; Ville et al., 1998; Ville et al., 1995).

Therapeutic reduction amniocentesis is the most widely available treatment for TTTS. In this treatment, a needle is inserted into the amniotic sac of the recipient twin under the guidance of ultrasound, and excess fluid is drained. This procedure reduces

the pressure in the womb, equalizes fetal development, and diminishes the risk of preterm labor and spontaneous rupture of the membranes. Survival rates with the use of amniocentesis therapy range from 33% to 83% (Farley et al., 2000; Mari et al., 2001). In another treatment, amniotic septostomy, a hole is created in the membrane between the amniotic sacs, allowing fluid from the recipient's sac to enter that of the donor. This procedure carries an increased risk of neurological injury to the fetuses and the greater possibility of complications (Allen et al., 2000; Farley et al., 2000; Hecher et al., 1999; Mari et al., 2000). In addition to these procedures, medications, such as Digoxin, are often administered from the time of the initial diagnosis in an attempt to prevent fetal heart failure, curtail the production of amniotic fluid, or stop premature labor.

Studies have demonstrated that the presence of TTTS and the resulting IUGR have a lingering adverse effect on the physical growth of affected infants (Fitzhardinge & Steven, 1972a, 1972b; Henrichsen, Skinhøj, & Anderson, 1986; Sung, Vohr, & Oh, 1993). However, the results of studies that have examined the effect of TTTS and IUGR on developmental outcomes have not been as definitive. It appears that infants who have not experienced the most severe complications of TTTS tend to develop comparably to full-term infants on developmental measures (Blair & Stanley, 1990; Paz et al., 2001; Peleg et al., 1998; Resnik, 2002; Sung, Vohr, & Oh, 1993; Van der Reijden-Lakeman, de Sonneville, Swaab-Barneveld, Slijper, & Verhulst, 1997; Vossbeck, deCamargo, Grab, Bode, & Pohandt, 2001; Wienerroither, Steinder, Tomaselli, Lobendanz, & Thun-Hohenstein, 2001). The worst outcomes have been observed in the most severely growth-restricted infants who were born preterm and exhibit the most overt evidence of impaired umbilical flow resulting in neurologic, cardiac, renal, or endocrine dysfunction (Farley et al., 2000; Fattal-Valevski et al., 1999; Jones, Sbarra, & Centrulo, 1998; Leonard, Piecuch, Ballard, &

Cooper, 1994; Mari et al., 2001; Resnik, 2002; Vossbeck et al., 2001; Wienerroither et al., 2001; Zach & Ford, 2002).

## Preterm birth

The literature has documented that preterm infants are not at an equal risk when it comes to developmental outcomes. Whereas infants who are born prematurely but are basically healthy and free from medical or neurological complications (low risk) tend to develop comparably to full-term infants on developmental measures (regardless of their gestational age or birth weight), high-risk infants exhibit persistent developmental delays (Anderson et al., 1995; Case-Smith, 1993; Jeng, Yau, & Teng, 1998; Kalmar & Boronkai, 1991; McCarton, Wallace, Divon, & Vaughan, 1996; O'Callaghan et al., 1995, 1996; Piper, Darrah, Byrne, & Watt, 1990).

Although there are no absolute criteria for identifying premature infants who are at the highest or lowest risk for developmental complications, the literature has documented some common factors (Fletcher et al., 1997). Low-risk infants are generally considered to be those who are healthy and have no major medical, neurological, or congenital abnormalities. In contrast, the smallest, sickest infants are considered to be at the highest risk. They typically have at least one medical risk factor associated with premature birth that requires the most invasive medical procedures. As a result, they are considered to be at a high risk for future developmental and medical disorders (Parmelee & Cohen, 1998). The severity of medical risk factors that are associated with preterm birth has a great impact on development, correlating inversely with the severity of the factors involved, including days on ventilation; the presence of chronic lung disease, hyperbilirubinemia, sepsis, necrotizing enterocolitis, apnea or bradychardia, intraventricular hemorrhage, periventricular leukomalacia, respiratory distress syndrome, or

patent ductus arteriosus; and the number of transfusions (Farley et al., 2000; Korner et al., 1993; Slaman-Forsythe, 2000; Thompson et al., 1994).

## Visual impairment

Infants affected by TTTS are at risk of developing visual impairment or blindness caused by retinopathy of prematurity resulting from preterm birth. Vision plays an important role in children's efforts to organize and give meaning to their environment. The potentially negative impact of blindness on an infant's development in the motor, socialization, and self-help domains has been well documented (Ferrell, 1986, 1998; Pérez-Pereira, 1994, 1999; Pérez-Pereira & Castro, 1997; Pérez-Pereira & Conti-Ramsden, 2000; Reynell, 1978; Warren, 1984). At particular risk in the cognitive domain are specific competencies in abstract thinking, spatial organization, object permanence, object constancy, and cause and effect (MacCluskie, Tunick, Dial, & Paul, 1998; Ross & Tobin, 1997; Troster & Brambring, 1993, 1994). Ferrell (1998) suggested that the sequence of development in several domains differs for children with visual impairments and that these unique patterns of development are predictable.

## Methodology

### Subjects

The subjects in this study were 24-month-old, monozygotic twin boys who were born at 26 weeks gestational age and were diagnosed with severe TTTS at 18 weeks gestation. Several treatments were attempted in utero, including reduction amniocentesis (at 22 weeks gestation), at which time 1 liter of excess amniotic fluid was removed from the sac of the recipient twin; prenatal antibiotics were administered; and laser fetoscopy, which was complicated by a tear of their amniotic membrane, was

conducted. (Prior to the fetoscopy, ultrasound had detected no bladder or amniotic fluid in the donor twin. Within 24 hours of the procedure, the donor twin had bladder output and fluid building up in the sac.) As a result of the TTTS, the infants experienced a severe disparity in growth (greater than 25%). At birth, the donor twin weighed 1 pound, 2 ounces (520 grams), and the recipient twin weighed 2 pounds (907 grams). Both twins were diagnosed with ROP at birth. The donor twin had severe bilateral ROP, which regressed to Stage 5, resulting in total vision loss even though bilateral laser vitrectomy (the removal of vitreous, blood, or membranes from the eye) was performed four times and scleral buckles (a procedure that attempts to reduce the pressure on the retinal surface) was conducted. Neither procedure was successful in restoring his vision. The recipient twin's most severe visual diagnosis was Stage 3 ROP, which fully resolved.

The donor twin experienced bradycardia, bronchopulmonary dysplasia, Grade 2 interventricular hemorrhage, and respiratory distress and spent 12 days on a ventilator. In contrast, the recipient twin experienced none of these medical risk factors and spent only 3 days on the ventilator. In addition, the donor twin experienced more severe complications that are associated with TTTS than did the recipient twin. He was diagnosed with hypoglycemia (low blood sugar), hypothyroidism (deficiency of the thyroid hormone that helps regulate the heart rate, blood pressure, body temperature, and growth and development), and hydronephrosis (distention of the kidney with urine, possibly because of obstruction of the outflow of urine) that required surgery and he spent 12 weeks in the Neonatal Intensive Care Unit of Johns Hopkins Children's Center after birth. The recipient twin experienced hydrops (water in the body indicating that he was struggling and severely sick, a sign of heart failure) and required monitoring for cardiac complications, but experienced less severe complications associated with the TTTS and was discharged after 10 weeks.

Neither infant has any documented neurological damage or hearing loss. The recipient twin has never qualified for early intervention services. The donor twin currently receives home-based early intervention services, including speech therapy, vision services, and occupational and physical therapy. The twins live with both parents and three older brothers.

## Instruments

The Battelle Developmental Inventory (BDI; Newborg, Stock, Wnek, Guidibaldi, & Svinicki, 1988) is a standardized, norm-referenced, individually administered assessment of key developmental skills in the personal-social, adaptive, motor, communication, and cognitive domains. It was selected for this research because it allows adaptive administration (there is no required set of materials or toys) and scoring procedures. The reliability of the BDI has been well documented. Interrater reliability has been reported in the manual ranges from .70 to .99, with a mean item-by-item test-retest reliability for the BDI total score ranging from .71 to .99 and a mean item-by-item test-retest reliability of .88 (Newborg et al., 1988). Several researchers have reported the concurrent validity of the BDI with other well-known early childhood measures for samples that have included children with disabilities (Behl & Akers, 1996; Gerken, Elliason, & Arthur, 1994; Glascoe & Bryne, 1993; Snyder, Lawson, Thompson, Stricklin, & Sexton, 1993). (It should be noted that a revision of the BDI—the BDI-2—was published at the time of this research, but was not yet available for public use.)

Because of the lack of standardized instruments that are normed on young children who are visually impaired or that have contained a significant number of visually impaired children in their normed samples, the use of norm-referenced instruments with this population is often a problem. Trzasko (1992, p. 7)

stated that a comprehensive educational assessment of young children who are visually impaired should include both a standardized, norm- or referenced instrument "with visually biased items eliminated or modified depending upon the extent of the visual impairment and a comprehensive, developmental scale [sensitive to the developmental needs of children with vision loss] that indicates the child's level of skills and abilities." In addition, the use of norm- or criterion-referenced instruments in a developmental assessment should be viewed not as exclusionary, but as complementary. If these instruments are selected with care, together they can provide valuable information (Sacks & Silberman, 1998).

Therefore, in addition to the BDI, the Oregon Project for Visually Impaired Preschool Children (OR; Brown, Simmons, & Methvin, 1991) was administered to both twins. The OR is a criterion-referenced instrument that was designed specifically for young children with visual impairments with developmental ages of 0–6 years. It does not provide an overall score or developmental age-equivalent scores, but, rather, "estimated age functioning levels" in each of eight domains; cognitive, language, socialization, self-help, fine motor, gross motor, vision, and compensatory skills. Items that are dependent upon vision have been eliminated from other domains and appear collectively in a domain entitled "vision." (The vision domain was not administered.) The skills in each domain are developmentally sequenced and are arranged in the following age categories: B–1, 1–2, 2–3, 3–4, 4–5, and 5–6 years. All major skills, including the prerequisite skills for orientation and mobility and braille, are included. All assessments took place in the twins' home and were video recorded with the mother present throughout the sessions.

The Vineland Adaptive Behavior Scales—Interview Edition (VABS; Sparrow, Balla, & Cicchetti, 1984) was also used for both twins. The VABS was designed to assess the personal and

social functioning of disabled and nondisabled persons from birth to adulthood. It is organized around four behavior domains: communication (receptive, expressive, and written), daily living skills (personal, domestic, and community), socialization (interpersonal relationships, play and leisure time, and coping skills), and motor skills (gross and fine).

The Interview Edition includes 297 items and provides a general assessment of adaptive behavior. It was administered to the twins' mother in a semistructured interview format, making it easy to gather a perspective of the twins' skills. The VABS provides an adaptive behavior composite score that summarizes each subject's performance in all four domains.

The instrument provides percentile ranks and stanines (for the domain and composite scores), adaptive levels (by percentile groups), and age equivalents (by raw score conversions). Split-half and test-retest reliability coefficients for the composite scores ranged from median values of .83 for the motor skills domain to .94 for the composite. Interrater coefficients are lower for the same measures: .62 to .78. Selected standardization subgroups were compared on the VABS, the K-ABC (Kaufman Assessment Battery for Children), and the PPVT-R (Peabody Picture Vocabulary Test-Revised). These concurrent measures exhibited low-to-moderate correlations, with generally higher coefficients obtained when the comparisons were made on subjects with handicapping conditions. The VABS was standardized on a representative national sample that included 3,000 subjects who were selected to match data from the 1980 U.S. census. The sample was stratified for age, race, gender, region, parental education, and community size. The VABS is recommended for assessment in clinical and research settings.

## Results

It should be noted that while the BDI provides raw and standard scores as well as percentile ranks, the OR provides "estimated age functioning levels" only. Therefore, although all available scores on both instruments are presented in Tables 1 and 2, for the purpose of comparing outcomes on both measures, age-equivalent scores will be discussed.

Table 1 presents a summary of scores on the BDI for each subject, including raw scores, percentile ranks, and  $z$  and  $T$  scores, as well as age equivalents in each domain. The donor twin achieved an overall age-equivalent score of 21 months on the BDI and demonstrated delays in the cognitive, adaptive, and gross and fine motor domains. On closer examination of the items missed in these domains, issues related to instrumentation began to emerge. For example, the donor twin received partial or no credit for six items in the cognitive domain. Four of the items (such as "explores environment visually" and "follows a visual stimulus") required vision and could not be adapted, and, as a result, he received no credit for those items. In the gross motor domain, the donor twin received partial or no credit for five items. (All five items are contained in the OR in subsequent age ranges, indicating that they are skills that children who are visually impaired typically acquire later.) The fine motor domain on the BDI is comprised of two subdomains: "fine muscle" and "perceptual motor." In the fine muscle subdomain, the donor twin achieved full credit for all items in the 0–24-month range (and one item in the 36–47-month range). However, of the five items in the perceptual motor subdomain, he received no credit for two items that required vision and could not be adapted, full credit for one item ("reaches for object placed before him/her and touches it"), and partial credit for the other ("builds a tower of 2 cubes," which, according to the OR, children who are totally blind typically acquire later).

The recipient twin achieved an overall age-equivalent score of 33

months on the BDI and demonstrated age-equivalent scores that were higher than his age level in every domain. A close examination of both twins' scores in the communication domain revealed that in overall communication, as well as in the expressive and receptive subdomains, both twins demonstrated skills that were at or above their age levels.

A summary of scores on the OR for each twin is presented in [Table 2](#), including the total number of skills and the number and percentage of skills attained in each domain (within each age range). The donor twin demonstrated skills that were at or above his age level in the cognitive, language, and social-emotional domains. However, in the self-help, fine motor, and gross motor domains, he demonstrated skills that were below his age level. The recipient twin demonstrated skills that were above his age level in the social-emotional, self-help, gross motor, fine motor, language, and cognitive domains. The vision and compensatory domains were not administered to the recipient twin.

The outcomes on the BDI and the OR for both twins were compared with regard to the twins' age functioning in each domain, since the OR does not provide percentile rank or  $z$  or  $T$  scores. The results for the donor twin were comparable on both instruments in the communication-language, adaptive-self-help, and personal-social domains. (The communication-language domain was compared with regard to the overall outcome because the OR does not delineate subdomains for receptive and expressive language skills.) The results for both twins on the BDI and OR differed significantly in the cognitive, gross motor, and fine motor domains. The results for the recipient twin were comparable on both instruments in the gross motor, fine motor, and cognitive domains. The donor twin demonstrated poorer outcomes in all domains than did the recipient twin, even when the age-functioning levels obtained through administration of the OR were taken into account. Since the OR contains a

compensatory skills domain that is not included in the BDI, no comparison of this area could be made.

Table 3 presents a summary of the results on the VABS–Interview Edition. It reveals a significant disparity between the twins' composite scores on adaptive behavior.

## Discussion

The purpose of this study was to compare the developmental outcomes of twins who were born preterm with TTTS and vision loss. The donor twin demonstrated poorer outcomes in all domains (on all instruments) than did the recipient twin. However, it is important to note that his developmental outcome is remarkable, given the severity and compounded nature of his medical conditions and vision loss.

Although the BDI provides suggested modifications for use with children who are visually impaired and allows for flexible administration, it did not appear to reflect accurately the abilities of the donor twin in the cognitive, fine motor, or gross motor domains. Two factors appear to have contributed to this determination. First, a significant number of test items were dependent on vision and could not be modified. Second, since the instrument was not normed with visually impaired children, it does not reflect items that are typically delayed in these children.

The disparity in the developmental outcomes of the twins appears to be related to the severity of the medical circumstances of their preterm birth and TTTS. Although both twins were adversely affected by the medical complications that are associated with TTTS, preterm birth, and ROP, the severity of these conditions was different for each twin. The donor twin was subject to the most severe medical risk factors that are associated with preterm birth and TTTS, as well as ROP that regressed to total vision loss,

whereas the recipient twin (although premature) was basically healthy. Three compounding factors (TTTS, premature birth, and vision loss) appear to have influenced the developmental outcomes of the twins. It was beyond the scope of this study to tease out the ways in which each may have been responsible.

## Implications for the field

The literature indicates that children who are visually impaired are at a particular risk for delays in the motor, social, and self-help domains of development. The results of this study seem to support these findings. However, care must be taken in generalizing these findings because of the study's single-case design. The study also appears to illustrate the problematic nature of developmental assessment of visually impaired children. The lack of standardized measures that are appropriate for use with this population forces interventionists to adapt existing measures. As was illustrated in this study, this practice can be cumbersome and problematic. Interventionists must remain vigilant in their interpretation of the results of assessments for children who are visually impaired, so as to plan and deliver effective intervention programs.

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